REMARKS

The Examiner has rejected claims 1-11, 15-19, 27-28, and 46 under 35 U.S.C. § 103(a) as unpatentable over *Eberle* (Helvetica Chimica Act, 1975, 58(7), 2106-29), *Ferreiri* (U.S. Patent No. 5,580,855), *Lipton* (U.S. Patent No. 5,028,592), and *Kauvar* (U.S. Patent No. 5,786,336). *Official Action*, page 3. The Examiner believes that *Eberle* discloses that through "an appropriate selection of protective groups, the reagents to be used and the reaction sequence it is possible to increase the yield in a solution synthesis" of the lysine-proline-valine tripeptide (hereinafter "the KPV tripeptide" or "Lys-Pro-Val tripeptide"). *Office Action*, page 6. The Examiner further contends that, in view of the secondary references, it would have been merely routine optimization to synthesize a KPV tripeptide with increased yield. *Id.* Applicant respectfully disagrees.

First, the Examiner's reliance on *Eberle* is misplaced and cannot be used to establish a *prima face* case of obviousness. Because no translation of *Eberle* is available, the Examiner relies on the disclosures of record to ascertain its teachings. *Eberle* is allegedly directed to the synthesis of peptides and discloses the synthesis of diamide compounds of the KPV tripeptide. *Application* at ¶[0009]. The synthesis of *Eberle* is further described at ¶[0010] and Scheme 1 of the pending application. These are the only summaries of *Eberle* of record before the Patent Office.

The Examiner, however, believes the disclosures in the application at paragraphs [0051] and [0052] are also taken from *Eberle* and relies on them to establish a *prima facie* case of obviousness. *Office Action*, pages 3-4, 6. This is not the case. Rather, paragraphs [0051] and [0052] are statements directed to the claimed invention, and serve to provide a summary of the claimed methods. These paragraphs provide the following:

> It is shown, according to the invention, that a particular combination of synthesis steps and the use of a particular combination of protective groups make it possible to prepare KPV tripeptide diamide derivates, or a salt of such compounds, in a solution synthesis method with a final yield much higher than the yield obtained with the known state of the art methods, and such a method does not require any final purification step, such as for example via ion exchange chromatography.
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> It has been shown that an appropriate selection of the protective groups, the reagents to be used and the reaction sequence makes it possible to increase the yield, in a solution synthesis, from 33% (Eberle et al., 1975) to more than 70% in the case of Ac-Lys-Pro-Val-NH_2.

Application, ¶¶ [0051], [0052], emphasis supplied. There can be no mistake that these passages refer to the methods of the claimed invention, and provide an overview of the procedures used and results obtained. This is especially true in view of the underlined passages which specifically compare the present invention with the known art, and *Eberle* in particular.

More importantly, these passages do not teach the ordering of reaction sequences or the selection of protective groups. Nor do they provide a suggestion that the methods of *Eberle* can increase reaction yield.

Moreover, Applicant has not made any statements during prosecution, as alleged by the Examiner, that *Eberle* teaches the possibility of increasing reaction yields. *Office Action*, page 4. Specifically, the Examiner states that "Applicant noted on page 17 of the response with the RCE, [that] Applicant did not per se find any increased yields via his process, but merely noted that *Eberle* et al. teach that is possible." *Office Action*, page 4. Applicant has made no such statements during

prosecution, but rather simply reiterated the disclosure of ¶[0052] in the prior response. There simply is nothing on the record which suggests that *Eberle* discloses increasing KPV tripeptide reaction yields. The claimed invention provides for increased yields over *Eberle*. *Eberle* does not disclose increasing its own yield. Accordingly, the Examiner has not established a *prima facie* case of obviousness.

When properly considered, *Eberle* teaches a convergent synthesis of a KPV tripeptide, where two starting materials, namely a Pro-Val-NH_2 dipeptide and a Boc-Lys(MSOC)-OH compound, are first prepared separately. *Id.* The two compounds are then coupled together followed by removal of the -Boc protecting group, acetylation on the Lys residue, and removal of the -MSOC group. *Id.*

In contrast, the claimed invention is directed to a linear synthesis of Ac-KPV-NH_2, *i.e.* building the KPV backbone, starting by reacting lysine with proline, and adding or removing protecting groups and reagents when necessary to achieve the appropriate functionality of the final KPV tripeptide.

Eberle neither teaches such a linear synthesis nor the unique protection/deprotection scheme of the claimed invention, used in this completely different synthetic scheme. There simply is no disclosure in *Eberle* to teach one skilled in the art to synthesize a funtionalized KPV tripeptide through a linear synthesis, let alone with increased yields.

Nor do the secondary references cure this deficiency. The Examiner believes that *Ferreira* teaches optimization of the methods of *Eberle* because (a) *Ferreira* teaches the solid-phase synthesis of Lys-Pro-Thr using a "scaffold that ironically use[s] a diamine cross-linker", and (b) *Ferreira* cites to another, different reference authored by *Eberle*. *Office Action*, pages 4-5, and 6. Even if the Patent Office were correct that *Ferreira* improves on *Eberle*, that fact would be of little

consequence as *Eberle* does not teach anything like the claimed methodology. Indeed, improving one unique method offers no insight into a completely unrelated method.

Ferreira discloses peptides, their synthesis, and their use as analgesics. One peptide disclosed by *Ferreira* is a KPV tripeptide or the C-terminal amide thereof, *i.e.* H-Lys-Pro-Val-NH_2. See *Ferreira* Col.2,ll.39; and col.3,ll.61-62. *Ferreira*, however, does not disclose a KPV-tripeptide diamide or the acetylated derivative Ac-KPV-NH_2, as in the claimed invention. Nor is there any teaching in *Ferreira* to arrive at the diamide form or that such a form is desirable from a therapeutic standpoint.

Moreover, *Ferreira* only describes the synthesis of the H-KPV-NH_2 tripeptide via solid-phase synthesis. It does not disclose a solution phase synthesis of any KPV tripeptide. *Ferreira* also teaches the synthesis of the peptide starting from the C-terminal amino acid (*i.e.* coupling valine with proline, followed by reaction with lysine), while the claimed invention teaches N-terminal synthesis (*i.e.* coupling lysine with proline before coupling with valine). *Id.* at *Col.2,ll.52-60*. Thus, the teachings of *Ferreira* are diametrically opposed to the claimed invention and only teach an alternative method of making the compound H-KPV-NH_2. Accordingly, one skilled in the art would not have been motivated by the teachings of *Ferreira*, alone or in combination with *Eberle*, to arrive at the claimed invention.

Moreover, the Examiner's reliance on *Ferreira's* use of a diamine cross-linker is misplaced. *Office Action*, page 4. The diamine cross-linker of *Ferreira* merely attaches the peptide to the solid support resin in a solid-phase synthesis. It serves no purpose in the reaction other than as a scaffold and cannot be considered a reagent which is incorporated into the final tripeptide.

Nor does *Lipton* cure the deficiencies of *Eberle*. *Lipton* is directed to the synthesis of diacetyl KPV-tripeptides for the treatment of various cellular disorders. *Official Action*, page 5. As admitted by the Examiner, *Lipton* does not teach KPV-tripeptide diamide derivatives, such as Ac-KPV-NH_2. *Id*.

Moreover, *Lipton* teaches protection of each of the lysine amine groups with the same protecting agent. *Lipton Col*.8,ll.55-61. In the claimed invention, on the other hand, each amine is protected with a different group, allowing regioselective protection and/or deprotection, which is important in subsequent coupling steps.

Finally, one skilled in the art would not look to *Kauvar*, alone or in combination with *Ferreira*, *Lipton,* or *Eberle*, to arrive at the claimed method. *Kauvar* is directed to glutathione tripeptide analogues. Unlike like the claimed invention, *Kauvar* does not disclose KPV-tripeptide analogs or procedures for their synthesis, as admitted by the Patent Office. *Official Action*, page 6.

For the most part, *Kauvar* only discloses general peptide synthesis methods. For example, *Kauvar* provides that "[t]he tripeptide analogs of the invention or additional tripeptide analog members can be synthesized using means generally known in the art." *Kauvar Col.10,ll.30-34*. The only specific synthesis described in *Kauvar* is a method of synthesizing •-glutamyl-S-benzyl-cysteinyl-•-alanine. *See Kauvar* Scheme 1 and Example 6. The methods of synthesizing this specific tripeptide, however, cannot be adapted to synthesizing a KPV-tripeptide. For example, the synthetic methods described couple the cysteine and alanine residues first, followed by reaction with the glutamate residue, *i.e.* a C-terminal synthesis. In contrast, the claimed method is directed to a N-terminal synthesis, *i.e* reaction of a lysine residue with proline, followed by coupling with valine. Therefore, *Kauvar's*

synthesis proceeds in an opposite manner. Accordingly, one skilled in the art would not have been motivated by the teachings of *Kauvar*, alone or in combination with the other cited references, to arrive at the claimed method.

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: June 23, 2009 Respectfully submitted,

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